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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN, LEWIS & BOCKIUS LLP (SF)
2 PALO ALTO SQUARE
3000 El Camino Real, Suite 700
PALO ALTO, CA 94306

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,320	BAYER, ROBERT	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8,10-17,19-21,31-36,38,40,42-49,51,54,55,87-89,91,93,95-102 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,6,8,10-17,19-36,38,40,42-49,51,54,55,87-89,91,93,95-102 and 104.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid. Applicant's submission filed on 6-30-06 has been entered.

Claims 1-4, 6, 8, 10-17, 19-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are currently pending and are present for examination. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are now under consideration. Claims 22-30 remains withdrawn from consideration as being drawn to non-elected invention.

Applicants' arguments and amendments filed on 7-27-06 have all been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previous rejection of claims 54-55, 87-93, 95-106, under 35 U.S.C. 103(a) as being unpatentable over Seed et al. (WO 96/40881, 12-19-1996), or Kasha et al. (US 5,374,655, 12-20-1994), and Paulson et al. (WO 98/31826, 7-23-1998). Examiner has withdrawn the above rejection in since applicants have amended the above claims to include the same phrase as that seen in claim 1, *i.e.*, "wherein said first fucosyltransferase is eukaryotic, lacks a membrane anchoring domain and is a member selected from FucT-VI, FucT-VII, and combinations thereof".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a general method of modifying the glycosylation pattern of a glycopeptide using a fucosyltransferase (FT) such as FucT- VI, or VII comprising an acceptor moiety and a donor moiety on a glycopeptide such that the glycopeptide is fucosylated, does not reasonably provide enablement for such a method for modifying the glycosylation pattern of a glycopeptide using exclusively a first fucosyltransferase wherein said first fucosyltransferase is eukaryotic, lacks a membrane anchoring domain and is a member selected from FT- VI, VII and combinations thereof and optionally using a second fucosyltransferase (with or without any limitation regarding its transmembrane domain) to fucosylate a second fucosylation site, wherein the glycopeptide is substantially uniformly fucosylated, or at least 80% of the acceptor moieties on the glycopeptide are fucosylated, or wherein a recombinant glycopeptide is substantially identically fucosylated as the wild type (non-recombinant) glycopeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are so broad as to encompass a method of using any fucosyltransferase or any FucT-VI, or VII including mutants, variants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of extremely large number of enzymes broadly encompassed by the claims and furthermore because of the characteristic nature of fucosyltransferases to altogether lose their specific ability to transfer fucose when the transmembrane domain in removed. Because of this unique characteristic nature of fucosyltransferases and also due to the fact that the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, it requires a knowledge of and guidance with regard to which specific fucosyltransferase can be used in the above method without its transmembrane domain as well as which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those fucosyltransferase enzymes lacking transmembrane domain and specifically have the properties of substantially uniformly fucosylating a glycopeptide, or at least fucosylating 80% of the acceptor moieties on the glycopeptide, or is capable of fucosylating a recombinant glycopeptide substantially identical to the wild type (non-recombinant) glycopeptide. While fucosyltransferases are known and

available in the art, enzymes endowed with above properties are not. Therefore it would require undue experimentation of the skilled artisan to make and use any fucosyltransferase for the above claimed method. The specification is limited to teaching the method using, perhaps specific variants or mutant FTs which are capable of above activities but provides no guidance with regard to the making of such variants and mutants or with regard to identifying such variants. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility for use in the above method are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of any FTs because the specification does not establish: (A) that any FT lacking transmembrane domain can be used in the above method; (B) regions of the protein structure

which may be modified in order to obtain an enzyme having above special activity; (C) the general tolerance of FTs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residues in any FT with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any FTs or any variants with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of FTs having the desired biological characteristics for the above method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection. Applicants have argued that they have limited the claims to two FTs, FT-VI and VII and provide a lengthy explanation regarding the efficacy of the claimed method. Examiner would like to reiterate here that the enablement rejection is not questioning the efficacy of the method but the scope of the enzymes used for the method. With reference to the question of enzymes used in the method, applicants argue that the specification teaches that FTs can lack transmembrane anchoring domain and such enzymes can be readily made by those skilled in the art and that FT-VI and FT-VII and combinations thereof can be used for the claimed method. Applicants also

argue that the specification enumerates a sufficient number of readily available fucosyl transferases including preferred fucosyltransferases that can be useful for the methods provided by the present invention as well as provides ample examples to demonstrate the operability and success of the claimed methods achieved by following the teaching and guidance provided by the present invention. Applicants also refer to the Wyeth and Avant studies directed to obtaining uniform fucosylation patterns via practicing the methods taught by the present invention is a further validation of the enabling teaching provided by the present invention. Examiner acknowledges applicant's arguments as well as the Thomas et al. publication, which applicants have referred to. Examiner respectfully reiterates that all the above arguments in no way overcome the enablement rejection. This is because, as stated clearly in the rejection, the claims are directed to the method of use of any or all FT-VI and VII enzymes including any variants and mutants, which indeed may lack membrane-anchoring domains. The art and the specification may teach where to obtain FTs as well as methods to remove membrane-anchoring domains. However, none of that can be a guidance for one skilled in the art to practice the method because, the specification is first of all silent on how to make the variants, mutants and recombinants from any given FT and second, the specification is totally silent on whether any such variant lacking membrane anchoring domain would continue to function as the original FT. Arguments as to why an FT's function becomes altered when membrane-anchoring domain is removed have been explained by the applicants themselves in their previous arguments as well as by the Examiner. Therefore, without the required guidance one of ordinary skill in the art would be subject to undue experimentation. The Thomas et al. publication which applicant has referred to is limited to the use of a specific FT, a recombinant human FT-VI. The reference does not

show that any or all FTs or variants, mutants and recombinants of that specific enzyme continue to have the same property after the removal of membrane anchor domain. Therefore the reference of Thomas et al. does not in any way remedy the enablement issue.

Applicants also disagree with the Examiner's argument that fucosyltransferases have a characteristic nature of altogether losing their specific ability to transfer fucose when the transmembrane domain is removed. (Page 4, lines 17-21). Examiner would again like to remind applicants that it was they who made that argument in response to the obviousness rejection in the previous Office action. While applicants may disagree now, they have provided no scientific argument to support their disagreement. If applicants have indeed found a specific FT-VI and VII enzyme that continues to exhibit its full original activity even after removal of the transmembrane domain then, limiting their claims to those specific enzymes would overcome (only) this rejection. However, until then the above rejection is maintained.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are directed to a method of fucosylation using polypeptides lacking transmembrane domain and further having the properties of substantially uniformly fucosylating a glycopeptide, or at least fucosylating 80% of the acceptor moieties on the glycopeptide, or is capable of

fucosylating a recombinant glycopeptide substantially identical to the wild type (non-recombinant) glycopeptide, or is capable of large-scale fucosylation of a glycopeptide. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 54-55, 87-89, 91, 93, 95-102, 104 are rejected under this section of 35 USC 112 because the claims are directed to a method of use of a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of the polypeptides as fucosyltransferases or fucosyltransferases lacking membrane anchor domain, has been provided by applicants, which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides, which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicant has traversed the above rejection arguing that the above rejection was previously withdrawn by Examiner but has now been reinstated and that it conflicts with the policy of the Office. Examiner is not aware regarding any such Office policy where a rejection once withdrawn cannot or should not be reinstated. In the instant case, Examiner has clearly explained in the previous Office action as to why this rejection has been brought back or reinstated. The rejection was brought back by the Examiner because of the applicant's arguments made against the obviousness rejection and their questioning of the legality of the use of the references of Costa et al. and Natsuka et al. Applicants clearly argued that it would not be obvious to one skilled in the art to use any or all FTs because of the teachings of Costa et al. or Natsuka et al. implying that the enzymes used in the claimed method is one of a class. Because of that requirement, Examiner is requiring the applicants to provide the structure of those enzymes that can be used in the claimed method. As of now claims are drawn to a method of use of enzymes whose structure has not been described by the applicants as explained in the above rejection. Hence the above rejection is maintained.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

December 5, 2006